

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

FLUOMETURON

Tolerance #229; Chemical Code # 000166  
SB 950-311

August 7, 1986  
Revised January 6, 1988  
Revised October 25, 1989

I. DATA GAP STATUS

Combined rat: (chronic + onco)	No data gap, possible adverse effect
Chronic dog:	No data gap, no adverse effect
Onco mouse:	No data gap, possible adverse effect
Repro rat:	No data gap, no adverse effect
Terato rat:	No data gap, no adverse effect
Terato rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotox:	Not required at this time

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Note: CDFA one-liners are attached

\*\* indicates acceptable study

**Bold face** indicates possible adverse effect

File name T891025

Revised: M. Silva, 10/89

The one applicable EPA one-liner is included.

Rectified through: 038/075546

## II. TOXICOLOGY SUMMARY

## COMBINED, RAT

## Subchronic Study

**033 072520** "90-Day Oral Toxicity Study in Rat with Fluometuron Technical", (conducting laboratory not specifically mentioned, report CF-742 submitted by Ciba-Geigy, March 12, 1965). Cotoran technical was administered in the diet at concentrations of 0, 100, 1000, or 10000 ppm to 15 CFE albino rats/sex/group for 90 days. NOEL = 100 ppm. UNACCEPTABLE and not upgradeable. Insufficient clinical chemistry examination, too few animals observed for hematological examinations, no ophthalmological examination, no analysis of dosing substance etc. **Adverse effect is indicated; splenic pathologies** in 9/15 male rats was observed at  $\geq 1000$  ppm. (JSK & M. Silva, 8/29/89).

## Combined Study

**\*\*018 054902** "Two-Year Chronic Oral Toxicity Study in Albino Rats," Fluometuron Technical-Final Report," (Hazleton, 8-18-82). Fluometuron technical, 96.1%, was administered in the diet to Fischer 344 CD-F rats 60/sex/group, for 2 years at 0, 10, 300 or 1000 ppm. 5/sex-control and 1000 ppm were sacrificed at 52 weeks. Another 5/sex-control and 1000 ppm were used for recovery after 52 weeks, then sacrificed at 60 weeks. Lower body weights were observed in both sexes at 1000 ppm during the first year. Treatment related decreases in hematocrit, hemoglobin and erythrocyte counts were observed at 1000 ppm in both sexes. **Adverse effect indicated.** An increased amount of hemosiderosis in spleen in 300 and 1000 ppm treated males and females and in livers from 1000 ppm treated males and females was observed. No oncogenic effect of fluometuron was observed. NOEL = 10 ppm. Initially reviewed as unacceptable (M. Silva, 12/22/87) since there was no ophthalmologic exam or hematology, clinical chemistry or urinalysis for 10 and 300 ppm at 26 and 52 weeks. Upon submission of additional information, the study has been re-reviewed and upgraded to **acceptable**. M. Silva, 7/24/89.

## CHRONIC, RAT

## Chronic Study

002 024961, "Examinations on Rats of the Chronic Toxicity of Preparation BA-27'690." (1966, Battelle Inst.) Fluometuron: no purity stated. Dosages of 0, 3, 10, 30 or 100 mg/kg/day by oral gavage 6X/week for approximately 53 weeks; No evidence of adverse effects, however insufficient information to establish a NOEL. UNACCEPTABLE. NOT UPGRADEABLE. Insufficient histological examinations, insufficient analysis of blood and urine parameters, too little individual data, etc. (Aldous, 8-7-86).

## CHRONIC DOG

## Subchronic Study

**033 072520** "90-Day Oral Toxicity Study in Dog with Fluometuron Technical", (AME Associates. Princeton, NJ, Report no. CF-743, April 26, 1965). Cotoran Technical administered in the feed at concentrations of 0 (diet only), 40 (1.5 mg/kg/day), 400 (15 mg/kg/day) or 4000 ppm (150 mg/kg/day) for 90 days to 3 Beagle dogs/sex/group. NOEL = 400 ppm/day. **Possible adverse effect** (congestion of livers, kidneys and spleen; hemosiderin deposition in spleens). UNACCEPTABLE not upgradeable. Insufficient information, too few animals, no analyses of dosing substance, etc. (JSK & M. Silva, 8/30/89).

## Chronic Study

\*\* 025 068693, "Fluometuron Technical: 1-Year Oral Administration to Dogs (Min 832047)", (CIBA-Geigy Corporation Pharmaceuticals Div., Laboratory Study No.832047, May 25, 1988). Fluometuron, purity 95.8%, administered in the feed at concentrations of 0, 20, 400 or 7000 ppm to Beagle dogs, 5/sex/group for 52 weeks. Three extra/sex dogs in the control and the high dose groups were continued an additional 4 weeks without further treatment and served as the recovery group. No adverse effect. NOEL = 400 ppm (Increased incidence of emesis; stool irregularities - diarrhea, mucous, soft and bloody stools; reduced body weight (14-19% less than control at week 52), body weight gain and feed consumption; reduced erythrocytic parameters and indices - HGB, RBC, HCT, MCV and MCHC; and increases in percent Heinz bodies, Howell-Jolly bodies and reticulocytes; reduced biochemical parameters - SGPT, glucose and increased cholesterol, bilirubin, potassium and inorganic phosphorous levels). Reduced HGB, increased platelet count and WBC for the recovery group. **ACCEPTABLE.** (JSK & M. Silva, 8/30/89).

## ONCOGENICITY RAT

See above: RAT, COMBINED

001 945204, "Bioassay of Fluometuron for Possible Carcinogenicity - Rat." (1980, Gulf Southern Research Inst.) Fluometuron 99+% purity indicated. Dosages of 0, 125 or 250 ppm in diet for 103 weeks; UNACCEPTABLE, incomplete- MTD not demonstrated, too few dose levels, no individual histopathology data, grade of test article not given, other deficiencies indicated on worksheet. (Aldous, 8-19-85).

## ONCOGENICITY MOUSE

\*\* **017 054901**, "Twenty-Four-Month Carcinogenicity Study in Mice." (Hazleton, 8-18-82 Revisions 1-28-83, 9-4-84 and 9-23-86.) Fluometuron technical, batch FL-780110, 96.1%, was administered to CR CD-1 mice, 60/sex/group for 104 weeks in the diet at 0, 10, 500 or 2000 ppm. Both sexes experienced lower body weight at 2000 ppm and cyanotic conjunctivae at 500 and 2000 ppm. **Possible adverse effect.** Males at 500 or 2000 ppm had an increased incidence in lung primary pulmonary neoplasia and at 2000 ppm, an increased incidence of amyloidosis in several organs. NOEL = 10 ppm. Females had increased lymphocytic lymphoma at 2000 ppm. Originally reviewed as unacceptable (M. Silva, 12/22/87), the requested historical control data of the incidence of lung tumors and lymphocytic lymphomas in CD-1 mice and results from the diet analysis were received at CDFA and evaluated. Currently, the study is complete and **acceptable.** M. Silva, 7/25/89.

033 072522. Supplement to 054901

**001 034796**, "Bioassay of Fluometuron for Possible Carcinogenicity - Mouse." (1980, Gulf Southern Research Inst.) Fluometuron 99+% Dosages of 0, 500 or 1000 ppm in diet for 103 weeks. **Adverse effect indicated.** Marginal but statistically significant increase in male hepatocellular adenomas and carcinomas; UNACCEPTABLE, incomplete, not upgradeable. MTD apparently not achieved, too few dose levels, no individual histopathology data, control group unrealistically small. (Aldous, 8-19-85).

## REPRODUCTION, RAT

\*\* 019 054903, "A Three Generation Reproduction Study in Albino Rats. Fluometuron Technical-Final Report." (Hazleton, 8-18-82) Fluometuron technical, 96.1 to 96.2%, was administered continuously in the diet nine weeks prior to mating, during 3 weeks of mating, then through gestation and weaning

(18 weeks total-both sexes), to Sprague-Dawley rats for a 3 generation, 2 litters/generation study. Dose levels were 0, 10, 300 or 1000 ppm, with 8 males and 16 females/treatment level. Parental and weaned pup NOEL = 10 ppm. No adverse effect. Gross and microscopic splenic pathologies in P<sub>1</sub>, P<sub>2</sub>, P<sub>3</sub> and F3 at 300 and 1000 ppm. Reproductive NOEL > 1000 ppm. No reproductive effects in males or females were observed in 3 generations. Originally reviewed as unacceptable, upon receipt of information regarding males and mating as well as information on the chemical concentration of fluometuron in diet, the study was re-reviewed and is now **acceptable**. M. Silva, 7/25/89.

033 072523. Supplement to 054903.

#### TERATOGENICITY RAT

\*\*021 054905, "A Teratology Study of Fluometuron Technical in the Albino Rat." (Ciba-Geigy, 6-19-86) Fluometuron technical, batch FL-821838, was administered to mated Crl. COBS CD (SD) (BR) rats at 0 (3% cornstarch, 0.5% Tween 80), 10, 100, or 1000 mg/kg/day on days 6 to 15 of gestation, with 27 animals per group. Decreased food consumption, weight gain, (transient at 100 mg/kg/day) and darkened spleen were observed at 100 and 1000 mg/kg/day. Lethargy, ataxia, pale eyes and extremities, encrustments around eyes/nose/mouth, salivation, blood on vulva, enlarged spleen and darkened kidneys and liver were observed at 1000 mg/kg/day. Maternal NOEL = 10 mg/kg/day. Delayed renal development was observed at 100 mg/kg/day. At 1000 mg/kg/day reduced litter size, fetal weight, and increased incidence of centrum/vertebra not ossified were observed. Developmental NOEL = 10 mg/kg/day. Originally reviewed as unacceptable (M. Silva, 12/15/88), upon receipt of the requested information regarding analysis of fluometuron in diet, the study was re-reviewed and found **acceptable**. M. Silva, 7/25/89.

033 072524 Supplement to 054905.

011 039149, "Reproduction Study, (Test for Teratogenic or Embryotoxic Effects)." (1971, Ciba-Geigy, Ltd.) test article = C 2059, Cotoron<sup>R</sup> (grade, purity, etc. not presented). 0, 25, 100, and 750 mg/kg/day, gavage; NOEL apparently 100 mg/kg/day for developmental and maternal effects (decreased fetal weights in 250 and 750 mg/kg/day fetuses; decreased food consumption in 250 and 750 mg/kg/day dams); UNACCEPTABLE and incomplete. Insufficient information for further analysis. (Aldous, 7-14-86).

003 024962 One-sentence reference to 1971 Ciba Geigy study reviewed in #039149.

#### TERATOGENICITY RABBIT

\*\* 020 054904, "Fluometuron Technical a Teratology Study in Rabbits (MIN 852139)." (Ciba-Geigy Corp., Research Dept., Pharmaceuticals Division, (3-25-86) Fluometuron technical, Batch FL 821838, 95.8%, was administered to New Zealand White rabbits by gavage on days 7 to 19 of gestation at 0 (3% cornstarch and 0.5% Tween 80), 1, 10 or 100 mg/kg/day, 19/group. Maternal NOEL > 10 mg/kg, (abortions, decreased food consumption); Developmental NOEL >100 mg/kg, (No fetal toxicity) No adverse effects. Originally reviewed as unacceptable (M. Silva, 12/22/88), upon receipt of the pilot study as a justification for dose selection and an analysis of fluometuron for stability, homogeneity and concentration in corn starch containing Tween 80, the study has been upgraded to **acceptable**. M. Silva, 7/26/89.

033 072524. Supplement to 054904.

010 039148, "Teratology Study of Fluometuron Technical in New Zealand White Rabbits." (1984, Ciba Geigy Corp.) Fluometuron, tech. 0, 50, 500, and 1000 mg/kg/day, by gavage; no maternal toxicity NOEL (absolute liver weight increased at 50 mg/kg/day and above, decreased food consumption, weight gain, and stool output in 500 and 1000 mg/kg/day dams. Decreased fetal

weights, slight decrease in ossification in 1000 mg/kg/day group). No adverse effect indicated. UNACCEPTABLE: no more data requested. Registrant is committed to repeating the study. (Aldous, 7-15-85).

EPA one-liner: Minimum and Supplementary. Teratogenicity NOEL = 500 mg/kg (the 1000 mg/kg level could not be assessed for effects due to mortality). Fetotoxic NOEL < 50 g/kg (LDT). Maternal NOEL < 50 mg/kg (LDT).

#### GENE MUTATION

\*\* 030 070302 "Gene Mutation Test Salmonella/Mammalian-Microsome Mutagenicity Test", (Ciba-Geigy Limited, Basle, Switzerland, Lab. study no. 871498, 2/19/88). Fluometuron, purity 95.3%, tests were performed on Salmonella strains TA 98, TA 100, TA 1535 and TA 1537 with and without Aroclor-induced rat liver activation at concentrations of 0 (acetone), 20, 78, 313, 1250 and 5000 µg/0.1 ml/plate and then repeated to confirm results. Fluometuron did not statistically increase numbers of revertants and is thus, considered non-mutagenic under the conditions of this test system. The study is **acceptable**. (JSK, & M. Silva, 8/29/89)

009 039147, "Salmonella/Mammalian-Microsome Mutagenicity Test with C2059 (Fluometuron) (Test for Mutagenic Properties in Bacteria)." (Ciba Geigy 1979) TA1535, TA1537, TA98 and TA100: fluometuron, no purity stated; ± S9 at 0, 25, 75, 225, 675 and 2025 ug/0.1 ml; triplicate plates, 1 trial; incomplete- UNACCEPTABLE (missing data). No evidence of cytotoxicity or increased reversion rate. (Gee, 7/14/86).

016 Ciba-Geigy has agreed to provide information requested by Gee (7/14/86) regarding Study 009 039147 by June 30, 1987. Their letter (2/27/87) is in CDFA DPN/Volume # 229-016, however the information has not been received by CDFA as of December 20, 1987.

#### CHROMOSOME

\*\* 030, 038 070300, 075545 "Nucleus Anomaly Test in Somatic Interphase Nuclei of Chinese Hamster," (Ciba-Geigy LTD., 3/4/86). Fluometuron technical (batch #: Op. 412076, 98.6% pure), was administered by gavage in a nucleus anomaly test to chinese hamsters at 0 (vehicle = 0.5% CMC), 1000, 2000 and 4000 mg/kg (5-6/sex/dose) once/day for 2 consecutive days. Animals were sacrificed 24 hours after the 2nd application. Bone marrow smears were made for analysis of somatic interphase cells. No significant chromosome effects were observed with fluometuron treatment. Positive controls functioned as expected. **Acceptable**. M. Silva, 8/31/89.

#### DNA REPAIR

\*\* 030, 038 070301, 075546 "Autoradiographic DNA Repair Test on Rat Hepatocytes," (Ciba-Geigy LTD., 4/25/86). Fluometuron technical (98.6% pure, batch #: Op. 412076) was used on rat hepatocytes in culture at 0 (vehicle = DMSO), 4, 20, 100 and 500 ug/ml (4 cultures/dose) for 5 hours. No DNA-repair effects were observed at any dose level. Positive controls functioned as expected. **Acceptable**. M. Silva, 8/31/89.

#### NEUROTOXICITY

Not required at this time.